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Molecular Medicine and Development

Program/Abstract # 394

Mechanical forces from the fetal breathing-like movements are transduced via Satb1 and Myb during mouse and human lung organogenesis

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Members of the Kablar Lab employ a holistic approach that considers both, the mechanical influences from the environment to the developing lung (an ecological developmental biology approach) and, the molecular players that may be involved in the transduction of the mechanical signals from the respiratory musculature (e.g., stretch) to the alveolar epithelium. To that end, we describe the lung phenotype of Satb1−/− mice (Dr. Terumi Kohwi-Shigematsu) and Myb−/− mice (Dr. Jonathan Frampton). In both mouse nulls, the lung displays most of the criteria for the pulmonary hypoplasia. In addition, Satb1−/− mice have significantly decreased number of type I pneumocytes, suggesting a role for Satb1 in the type II-to-I transition. Our preliminary data suggest that CTGF is an important player in the human lungs as well.

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Program/Abstract # 395

A developmental switch yields a treatment for beta thalassemias and sickle cell disease

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Gene regulation of developmental hemoglobin switching may provide phenotypic cures for beta thalassemias and sickle cell disease since it has been shown that reactivation of fetal globin expression alleviates both disorders. We have discovered a protein that regulates this developmental switch. Ferritin heavy chain (FtH) represses adult β-globin expression and activates γ (fetal)-globin gene expression in embryonic/K562 erythroid cells (Broyles et al., PNAS 98: 9145, 2001), leading us to propose utilizing FtH as a therapeutic agent. FtH localizes to the nucleus in K562 cells and represses the human adult β-globin promoter in transient expression assays. ChIP assays using anti-FtH polyclonal antisera show that FtH is bound to a −150 promoter repression site in vivo in K562 cells in which the β-globin gene is repressed. An Alexa488-tagged antisense oligonucleotide to FtH transfected into K562 cells enters the nucleus and derepresses the β-globin gene. Strikingly, the anti-FtH oligo knocks down both FtH and γ (fetal)-globin gene expression by 90%, confirming FtH's role as an activator of fetal Hb. An FtH transgenic mouse which expresses human FtH in definitive erythroid cells produces mice born with reduced adult β globin. Recent experiments show that FtH activates γ (fetal)-globin gene expression, as well as represses β^S-globin, in maturing human erythroid precursor cells from pediatric sickle cell patients.

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Program/Abstract # 396

Rhabdomyosarcoma — A tumor balanced at a differentiation tipping point

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Rhabdomyosarcomas (RMS) are a pediatric solid tumor of skeletal muscle. RMS resemble cells that have committed to the myogenic lineage, but have not yet completed differentiation. RMS fail to differentiate even though they express the myogenic bHLH (basic helix–loop–helix) transcription factor MyoD, a factor sufficient to induce myogenic differentiation in multiple other cell types. The seeming paradox of MyoD's presence but the failure to differentiate led us to look for myogenic inhibitors in RMS. We have identified two bHLH factors that had previously been unknown to contribute to the undifferentiated RMS state: MSC (musculin/MyoR) and E2A-2/5 (a shortened splice form of the bHLH factor E2A). Both of these factors compete with MyoD activity in RMS and are present in normal, undifferentiated myoblasts. Remarkably, expression of a forced protein dimer of MyoD and full-length E2A (MyoD~E) differentiates a cell culture model of RMS and leads to the downregulation of numerous myogenic inhibitors, MSC and E2A-2/5 among them. This suggests that RMS represent an arrested state of normal myogenic development. MyoD~E induces expression of the myogenic microRNAs, miR-206 and miR-133b, and miR-206 is also sufficient to drive RMS differentiation in cell culture. Chromatin immunoprecipitation has identified MSC as binding to DNA upstream of miR-206 in RMS, suggesting that competition between activating and inhibitory bHLH proteins maintains the undifferentiated state of rhabdomyosarcomas.

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